

# **Exhibit M**

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/296621313>

# Long-Term Follow-Up of Individuals Undergoing Sex-Reassignment Surgery: Somatic Morbidity and Cause of Death

Article in Sexual Medicine · March 2016

DOI: 10.1016/j.esxm.2016.01.001

CITATIONS

9

READS

415

4 authors, including:



Gert Martin Hald

University of Copenhagen

74 PUBLICATIONS 2,139 CITATIONS

[SEE PROFILE](#)



Ellids Kristensen

University of Copenhagen

80 PUBLICATIONS 981 CITATIONS

[SEE PROFILE](#)



Annamaria G E Giraldi

Rigshospitalet

134 PUBLICATIONS 3,167 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Treatment of women with a history of CSA [View project](#)



Healthy sexual aging [View project](#)

# SEXUAL MEDICINE

---

## BASIC SCIENCE

### Long-Term Follow-Up of Individuals Undergoing Sex-Reassignment Surgery: Somatic Morbidity and Cause of Death



Rikke Kildevæld Simonsen, MA,<sup>1</sup> Gert Martin Hald, PhD,<sup>2</sup> Ellids Kristensen, MD, FECSM,<sup>3</sup> and Annamaria Giraldi, PhD, MD, FECSM<sup>3</sup>

#### ABSTRACT

**Introduction:** Studies of mortality and somatic well-being after sex-reassignment surgery (SRS) of transsexual individuals are equivocal. Accordingly, the present study investigated mortality and somatic morbidity using a sample of transsexual individuals who comprised 98% ( $n = 104$ ) of all surgically reassigned transsexual individuals in Denmark.

**Aims:** To investigate somatic morbidity before and after SRS and cause of death and its relation to somatic morbidity after SRS in Danish individuals who underwent SRS from 1978 through 2010.

**Methods:** Somatic morbidity and mortality in 104 sex-reassigned individuals were identified retrospectively by data from the Danish National Health Register and the Cause of Death Register.

**Main Outcome Measures:** Somatic morbidity and cause of death.

**Results:** Overall, 19.2% of the sample were registered with somatic morbidity before SRS and 23.1% after SRS ( $P = \text{not significant}$ ). In total, 8.6% had somatic morbidity before and after SRS. The most common diagnostic category was cardiovascular disease, affecting 18 individuals, 9 before and 14 after SRS, and 5 of those 14 who were affected after SRS had cardiovascular disease before and after SRS. Ten individuals died after SRS at an average age of  $53.5 \pm 7.9$  years (male to female) and  $53.5 \pm 7.3$  years (female to male).

**Conclusion:** Of 98% of all Danish transsexuals who officially underwent SRS from 1978 through 2010, one in three had somatic morbidity and approximately 1 in 10 had died. No significant differences in somatic morbidity or mortality were found between male-to-female and female-to-male individuals. Despite the young average age at death and the relatively larger number of individuals with somatic morbidity, the present study design does not allow for determination of causal relations between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality.

*Sex Med* 2016;4:e60–e68. Copyright © 2016, International Society for Sexual Medicine. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Key Words:** Follow-Up; Gender Identity Disorder; Somatic Morbidity; Sex-Reassignment Surgery; Transsexualism

#### INTRODUCTION

Transsexualism refers to a condition in which the core characteristic is an individual's experience of profound incongruence between assigned sex at birth and the experienced gender.<sup>1</sup> According to the *International Statistical Classification of*

*Diseases and Related Health Problems, 10th Edition (ICD-10)*,<sup>2</sup> the diagnostic criteria of transsexualism are (i) the desire to live and be accepted as the opposite sex, (ii) usually a sense of discomfort with or inappropriateness of one's anatomic sex, and (iii) a wish to have surgery and/or hormonal treatment (HT) to make the body as congruent as possible with the preferred sex. To develop characteristics of the opposite sex, treatment with cross-sex hormones (HT), castration, and genital reconstructive surgery (sex-reassignment surgery [SRS]) might be conducted.

The parent category of transsexualism in the *ICD-10* is gender identity disorder (GID).<sup>2</sup> In Denmark, individuals with GID are referred to the Gender Identity Unit, University of Copenhagen (GIUUC) under *ICD-8*<sup>3</sup> code 302.39 and 1993 *ICD-10*<sup>2</sup> codes DF64.0 to DF64.9 by a general practitioner or psychiatrist. Assessment, in accordance with Danish Health Authority

Received November 25, 2015. Accepted January 13, 2016.

<sup>1</sup>Department of Sexology, University Hospital of Copenhagen, Copenhagen, Denmark;

<sup>2</sup>Department of Public Health, University of Copenhagen, Copenhagen, Denmark;

<sup>3</sup>Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen, Denmark

Copyright © 2016, International Society for Sexual Medicine. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.esxm.2016.01.001>

## Transsexualism: Somatic Morbidity and Mortality

e61

guidelines,<sup>4</sup> includes blood sample analyses for chromosomal and hormonal abnormalities, screening for psychiatric and somatic morbidities, psychological testing, and sessions with a psychologist or psychiatrist.

If SRS is desired by the individual diagnosed with transsexualism, an observational period of at least 1 year 6 months (in the study period, 2 years), including 1 year of HT and living in the gender role as the opposite sex, is obligatory before applying for SRS to the Danish Health Authority. The Danish legal criteria for SRS and castration are an *ICD-10* diagnosis of transsexualism (F64.0), persistent wish for and understanding of the consequences of castration, and a minimum age of 18 years (during the study period, ie, 1978–2010, the minimum age was 21 years).<sup>5</sup> All treatment is paid for by the public Danish medical system. Treatment with cross-sex hormones and genital reconstructive surgery has existed for more than 60 years, but findings on mortality and somatic well-being after SRS in long-term follow-up studies are equivocal.<sup>6</sup> For possible somatic consequences of HT, the following outcomes have been studied the most: cardiovascular disease (CVD), bone growth, and hormone-sensitive cancer malignancies.

A review and meta-analysis of 16 studies, including 1,471 male-to-female (MtF) and 651 female-to-male (FtM) individuals, found no overall significant effect of HT on CVD.<sup>7</sup> However, the type of HT (ethynodiol diacetate) and the manner in which HT (oral estrogens) was administered in MtF patients were significantly associated with CVD.<sup>8,9</sup> Further, in a Swedish study, increased CVD mortality in FtM and MtF individuals at least 10 years after HT was found,<sup>6</sup> indicating a possible delay of adverse somatic consequences from HT on cardiovascular pathology.<sup>10</sup>

Studies of muscle and musculoskeletal diseases, bone growth, and bone deficiencies overall did not show an increased risk of osteoporosis in FtM individuals.<sup>11–16</sup> However, in MtF individuals, lower bone mass density, possibly from androgen deprivation, was found after treatment compared with before treatment with HT.<sup>17–19</sup> However, because of increased bone density before treatment and no loss of bone density from menopause, MtF individuals maintain a lower risk of osteoporosis than assigned women.<sup>20</sup>

In cancer studies involving transsexuals receptive of SRS and/or HT, the focus has been on breast cancer, although the overall number of studies in relation to this issue is limited. The conclusions emerging from these studies suggest that for MtF individuals<sup>20–23</sup> the risk of breast cancer is lower than the expected risk of breast cancer in assigned women but similar to that expected in assigned men. For FtM individuals, male sex hormones might have an antiproliferative effect on breast cancer cell lines.<sup>24,25</sup> Thus, few cases of breast cancer in FtM individuals have been reported,<sup>26,27</sup> indicating FtM individuals have similar risk as expected for male breast cancer.

Concerning cancer malignancies, a Belgian study, in which the average time of HT was 6 years (FtM) or 7 years (MtF), found

no increase in cancer malignancies among included transsexuals compared with controls randomly selected from the population.<sup>28</sup> In contrast, a Swedish study found borderline significant risk of death from neoplasms compared with controls.<sup>6</sup> Lifestyle habits such as smoking and avoidance of the health care system were suggested as possible mediating mechanisms.

When studying increased and decreased risks of cancer in transsexuals receiving HT, it is important to note that HT has been used for 60 years in some transsexual individuals. Accordingly, the duration of exposure to HT might not be long enough for tumors to manifest and the number of individuals exposed is small.<sup>29</sup> Further, it has been suggested that inconsistency in reporting cancer incidents among transsexuals might lead to an underreporting of cancer in this cohort,<sup>21,30</sup> likely affecting prevalence and incidence rates.

Studies of mortality in transsexuals have suggested an increased mortality risk compared with controls.<sup>6,10</sup> For example, a Swedish study of 324 MtF and FtM individuals after SRS (follow-up = 11.4 years) found that the all-cause mortality rate was three times higher in this cohort compared with controls.<sup>6</sup> Similarly, in a Dutch long-term follow-up study of 966 MtF and 365 FtM individuals (follow-up = 18.5 years), a 51% higher mortality rate was found in MtF subjects compared with the general population.<sup>10</sup> For FtM subjects, no increased mortality was found compared with the general population. A Dutch study of 1,109 individuals receiving HT found no increased mortality overall, but in MtF subjects 25 to 39 years old, mortality was significantly increased because of suicide, acquired immune deficiency syndrome, CVD, drug abuse, and unknown causes.<sup>31</sup> The only Danish study on transsexualism conducted thus far, which included 37 individuals, reported three deaths of 29 reassigned MtF individuals and no deaths of 8 FtM individuals studied from 1956 through 1978.<sup>32</sup>

Somatic morbidity after alcohol abuse has not been investigated previously, although studies of substance abuse in individuals with transsexualism have been conducted. A Belgian study (N = 35) conducted at the University Hospital of Gent found alcohol and drug abuse in 50% of MtF and 61.5% of FtM individuals.<sup>33</sup> A Spanish study (N = 230) of individuals with complaints of GID seen at the Hospital Clinic (Barcelona, Spain) found current alcohol- and substance-related disorders in 11% MtF and 1.4% of FtM subjects.<sup>34</sup> A Swiss study found that 45% of 31 GID individuals diagnosed by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*<sup>35</sup> had lifetime substance abuse (MtF = 50%, FtM = 36.4%).<sup>36</sup> A Swedish study of 233 individuals found substance abuse in 18.2% of FtM and 11.9% MtF individuals.<sup>37</sup> However, in a different Swedish study of 324 MtF and FtM transsexual individuals, no significant risk of being hospitalized for substance abuse was found compared with the general Swedish population.<sup>6</sup> Lung diseases related to or caused by smoking have not been investigated previously in persons with transsexualism, although lesbian, gay, bisexual, and transgender persons have a higher incidence of smoking.<sup>38,39</sup> Accordingly, this was included as an outcome in the present study.

For many of the studies that have focused on somatic morbidity and mortality, including those reviewed earlier, the following methodologic shortcomings apply: small sample, recruitment and diagnostic biases and inconsistencies (eg, place of participant recruitment and differences in diagnostic criteria), heterogeneity of treatment regimens, and varied duration of follow-up periods.<sup>6</sup>

The aim of the present study was to (re)investigate somatic morbidity and mortality using registry data in a cohort including 98% of all Danish individuals referred to a public GID clinic in Denmark who underwent SRS from 1978 through 2010 after a diagnosis of transsexualism.

## AIMS

The specific aims of the study were to investigate (i) somatic morbidity before and after SRS and (ii) cause of death and its relation to somatic morbidity.

## METHODS

### Procedure

The study was approved by the Danish Data Protection Agency and the Danish Health Authority. Permission was obtained from the Civil Law Board to identify names and social security numbers of individuals who underwent SRS from 1978 through 2010 and who were treated at the GIUUC.

### National Registers

The Danish National Health Register (LPR) was used to draw data on somatic morbidity. The LPR contains diagnoses and dates of onset and end of treatment of all somatic episodes at hospitals from 1977 (inpatients) and from 1995 (outpatients). In the LPR, diagnoses are coded according to the *ICD-8* (1969–1993) or *ICD-10* (1994–).<sup>2,3</sup> Data from the LPR from 1977 to January 2013 were included in the study.

The Cause of Death Register has recorded all deaths and causes of death in Denmark since 1970. Death events occurring up to April 2014 were included in the study.

### Study Population

Included in the study were 104 individuals (56 MtF and 48 FtM) diagnosed with transsexualism according to the *ICD-8*<sup>3</sup> or *ICD-10*<sup>2</sup> at the GIUUC. All participants underwent castration with permission from the Danish Health Authority from 1978 through 2010. Verification that an individual had undergone SRS was accomplished using social security numbers (ie, Danish Cause of Death Register numbers); numbers ending in even numbers indicate female-assigned sex and those ending with odd numbers indicate male-assigned sex. Accordingly, changes in this number from even to odd or vice versa indicate the official change of assigned sex (ie, successful completion of SRS). Baseline data (Table 1) were obtained from medical records.

**Table 1. Baseline Data**

Variables	Male to female (n = 56)	Female to male (n = 48)
Mean age at referral (y), mean (SD)	30.3 (9.8)	27.0 (8.7)
Mean age at permission for SRS (y), mean (SD)	37.1 (9.7)	32.6 (8.0)
Mean age at initiating cross-sex hormones (y), mean (SD)	32.0 (9.9)	29.8 (8.4)
Mean length of follow-up (y), mean (SD)	16.38 (7.1)	10.21 (6.1)

SRS = sex-reassignment surgery.

Sociodemographic data (Table 2) were obtained from medical records and are further described by Simonsen et al.<sup>40</sup>

Because of the lack of a specific code for SRS, the date of start of follow-up was defined as the date of permission to undergo SRS.

### Measures

Baseline data (Table 1) were obtained from medical records based on interviews performed by specialized psychiatrists, psychologists, and medical doctors at the GIUUC during the treatment period.

Using the LPR and death registers, we obtained information pertaining to somatic morbidity before and after permission to undergo SRS and time and cause of death after obtaining this permission. More specifically, somatic diagnoses given to the patient from 1977 to January 2013 were investigated. Accordingly, each individual could present with different diagnoses, but multiple contacts with the somatic care system with the same diagnosis only had one outcome before SRS and one outcome after SRS. In addition, data on time and cause of death after permission to undergo SRS were drawn from the death registers until April 2014.

For each diagnosis, specifically chronic heart disease (*ICD-10* diagnoses F400–490), chronic lung disease (*ICD-10* diagnoses J40–47, *ICD-8* diagnoses 490–493), cancer (*ICD-10* diagnoses C00–C97.9, D00–D10.9, *ICD-8* diagnoses 140–209), alcohol-related liver morbidity (*ICD-10* K70–77, *ICD-8* 303–304), or muscle and musculoskeletal diseases (*ICD-10* M80–85, *ICD-8* 720–729), individuals were stratified by diagnostic group membership (ie, had received the diagnosis or had not received the diagnosis) and assigned sex (ie, MtF or FtM).

Mortality was determined by the cause-of-death certificate. Hence, each individual was dead or alive. For death, data related to cause of death were drawn from the death certificate.

### Statistics

Statistical analyses were conducted in SPSS 19.0 (SPSS, Inc, Chicago, IL, USA). Clinical variables were analyzed using descriptive statistics. Means and SDs were calculated for

## Transsexualism: Somatic Morbidity and Mortality

**Table 2.** Sociodemographics by Male to Female and Female to Male\*

	Male to female (n = 58)	Female to male (n = 50)
Primary and secondary education (y), n (%)		
≤11	40 (69.0)	38 (76.0)
12–13 (completion of high school)	16 (27.6)	12 (24.0)
Missing information	2 (3.4)	0
Education beyond primary and secondary school at time of referral, n (%)		
None	29 (50.0)	30 (60.0)
≤3 y or apprenticeship	21 (36.2)	8 (16.0)
≥4 y	5 (8.6)	10 (20.0)
Unknown	3 (5.2)	2 (4.0)
Education beyond primary and secondary school when permission for SRS was granted, n (%)		
None	25 (43.1)	25 (50.0)
≤3 y or apprenticeship	21 (36.2)	13 (26.0)
≥4 y	8 (13.8)	10 (20.0)
Unknown	4 (6.9)	2 (4.0)
Employment at time of referral, n (%)		
Employed	36 (62.1)	31 (62.0)
Unemployed		
Sickness or unemployment benefits	12 (20.7)	7 (14.0)
Social welfare or pension	10 (17.3)	12 (24.0)
Employment when permission for SRS was granted, n (%)		
Employed	32 (55.2)	27 (54.0)
Unemployed		
Sickness or unemployment benefits	5 (8.6)	11 (22.0)
Social welfare or pension	20 (34.5)	11 (22.0)
Unknown	1 (1.7)	1 (2.0)

From Simonsen et al.<sup>40</sup>

SRS = sex-reassignment surgery.

\*The  $\chi^2$  and Fisher exact tests were conducted but showed no significance ( $P < 0.05$ ).

continuous variables. Frequencies and percentages were generated for nominal and categorical variables. Between-group differences were analyzed using  $\chi^2$  test, t-test, and Fisher exact test.

No missing values were found for somatic outcome variables because they were obtained from the register data, where values are present (affected) or absent (unaffected).

## RESULTS

Baseline data related to age at referral, permission for SRS, cross-sex hormonal initiation, and years of follow-up after SRS are presented in Table 1.

To investigate the first study aim concerning somatic morbidity before and after SRS, the total number of included

individuals who received a somatic diagnosis was identified (Table 3). As presented in Table 3, 20 FtM and MtF individuals (19.2%) before SRS and 24 FtM and MtF individuals (23.1%) after SRS had somatic morbidity, with no significant difference. Nine individuals (eight MtF and one FtM) had somatic morbidity before and after SRS, resulting in 35 individuals (33.7%) overall who had somatic morbidity. Table 4 lists the specific diagnoses of somatic morbidity.

As presented in Table 4, 25 somatic diagnoses were reported before SRS and 27 diagnoses after SRS from a total of 20 individuals before SRS and 24 individuals after SRS. Nine of the 24 individuals had somatic morbidity before and after SRS. The most common diagnostic category was CVD, affecting a total of 18 individuals, 9 before and 14 after (23 diagnoses) SRS, and 5 of the 14 individuals had CVD before and after SRS. The second most common diagnostic category was muscle and musculoskeletal diseases, with 12 diagnoses, six before and six after SRS, affecting a total of 11 individuals, with only one individual having muscle and musculoskeletal disease before and after SRS.

To investigate differences in somatic morbidity between MtF and FtM individuals,  $\chi^2$  test, Fisher exact, and t-test were used. Across diagnostic categories, no significant differences in somatic morbidity between MtF and FtM individuals were found. When comparing somatic diagnoses using  $\chi^2$  test, no significant differences between the number of somatic diagnoses given before and after SRS were found.

Concerning the second study aim, cause of death and its relation to somatic morbidity was investigated from after SRS until April 2014. Ten individuals (9.6%; six MtF [10.7%] and four FtM [8.3%]) died from after SRS to April 2014. Mean age at death was  $53.5 \pm 7.9$  years (median = 55.5) for MtF individuals and  $53.5 \pm 7.3$  years (median = 52.5) for FtM individuals ( $P > .05$  by t-test). Somatic morbidity (ie, official cause of death) included two suicides (19 and 26 years after SRS, respectively), heart disease (n = 2), cancer (n = 1), ulcer (n = 1), and smoking- and alcohol-related diseases (n = 4).

Because the results might be influenced by changes in clinical procedures and guidelines over time and the cultural acceptance of transsexualism, data were checked for systematic differences in permission to undergo SRS from the first 16 years (1978–1994) to the next 16 years (1994–2010). Significantly ( $P < .05$ ) more individuals with transsexualism received permission to undergo SRS from 1995 through 2010 (28 individuals in 1978–1994 and 76 individuals in 1995–2010).

## DISCUSSION

We report the first nationwide register-based SRS follow-up study in Denmark of 98% of individuals who officially underwent SRS from 1978 through 2010.

For the first study aim (ie, investigation of somatic morbidity before and after SRS), we found that 19.2% of the cohort had a somatic diagnosis before and 23.1% after SRS. This difference

**Table 3.** Individuals with Somatic Morbidity Before and After SRS\*

Diagnosis, n (%)	Before SRS		After SRS		Before and after SRS	
	Male to female (n = 56)	Female to male (n = 48)	Male to female (n = 56)	Female to male (n = 48)	Male to female (n = 56)	Female to male (n = 48)
Cancer	0	3	2	1	0	1
CVD	5	4	6	8	5	0
Musculoskeletal	3	3	3	3	1	0
Lung	2	1	3	1	2	0
Alcoholic liver	1	3	0	0	0	0
Individuals with somatic diagnosis						
Yes	8 (14.3)	12 (25.0)	12 (21.4)	12 (25.0)	8 (14.3)	1 (2.1)
No	48 (85.7)	36 (75.0)	44 (78.6)	36 (75.0)	48 (85.7)	47 (97.9)

CVD = cardiovascular disease; SRS = sex-reassignment surgery.

\*The  $\chi^2$  and Fisher exact tests were conducted but showed no significance ( $P < 0.05$ ).

was found not to be statically significant. Further, no significant difference in somatic morbidity between FtM and MtF cohorts was found. For the second study aim (ie, investigation of mortality), no significant difference in mortality between MtF and FtM cohorts was found. Average age at death was 53.5 years, and 10 individuals died after SRS.

For somatic morbidity, CVD was found in 6 MtF individuals (10.7%) and 12 FtM individuals (25.0%). In comparison, 4.4% of assigned men and 3.6% of assigned women older than 35 years in the general Danish population were found to have CVD.<sup>41</sup> In the present study, CVD might have been due to long-term follow-up after HT (16.3 years for MtF cohort, 10.8 years for FtM cohort) as reported by other studies,<sup>6,10</sup> or the

observed prevalence of CVD might be explained by a correlation between depression and anxiety and CVD as suggested by previous research.<sup>42,43</sup> Socioeconomic status and CVD are related,<sup>44,45</sup> and the present study group was characterized not only by anxiety and depression<sup>46</sup> but also by social marginalization<sup>47</sup> and difficulties in school, education, and employment.<sup>40</sup> Hence, these factors could be important underlying mediating and/or moderating mechanisms driving or affecting prevalence rates of CVD in transsexuals, although the design of this study did not enable us to explore this further.

Muscle and musculoskeletal morbidity was found in 11 individuals (10.5%). From 1997 through 2002, 13.9% of the general Danish population was diagnosed with muscle and

**Table 4.** Number of Somatic Diagnoses\*

Diagnosis, n (%)	Before SRS		After SRS	
	Male to female (n = 56)	Female to male (n = 48)	Male to female (n = 56)	Female to male (n = 48)
Alcohol related				
Yes	1 (1.8)	3 (6.2)	0	0
No	55 (98.2)	45 (93.8)	56 (100.0)	48 (100.0)
Cancer				
Yes	0	3 (6.3)	2 (3.8)	1 (2.0)
No	56 (100.0)	45 (93.8)	55 (98.2)	47 (97.9)
Heart				
Yes	5 (8.9)	4 (8.3)	6 (10.7)	8 (16.7)
No	51 (91.1)	44 (91.7)	50 (89.3)	40 (83.3)
Lung				
Yes	2 (1.8)	1 (2.1)	3 (5.4)	1 (2.1)
No	54 (96.4)	47 (97.9)	53 (94.6)	47 (97.9)
Musculoskeletal				
Yes	3 (5.4)	3 (6.3)	3 (5.4)	3 (6.3)
No	53 (94.6)	45 (93.8)	53 (94.6)	45 (93.7)
Positive somatic diagnosis	11	14	14	13

SRS = sex-reassignment surgery.

\*The  $\chi^2$  and Fisher exact tests were conducted but showed no significance ( $P < 0.05$ ).

musculoskeletal disease by hospital care.<sup>48</sup> Smoking and excessive alcohol consumption have been linked to low bone mass and increased fracture risk in MtF and FtM individuals,<sup>49,50</sup> and such lifestyle issues might characterize the present cohort.<sup>6,46,51,52</sup> However, given the limited number of individuals presenting with skeletal morbidity in this study, more comparable studies are needed to confirm the possible increased risk of skeletal morbidity in this cohort.

Concerning cancer malignancies, five individuals (6.2% of FtM and 3.6% of MtF) were found to have a diagnosis of cancer compared with 2.4% of assigned women and 1.56% of assigned men older than 15 years in the Danish general population.<sup>53</sup> Previous studies involving transsexual individuals have found hormone-sensitive tumors.<sup>16,20,54</sup> Further, in the present study, two deaths were caused by cancer and by leukemia and lung cancer, respectively. However, as in the present study, small samples and the sample design preclude causal inferences regarding relations between treatment of SRS individuals and cancer or cancer-related deaths.

In Denmark, alcohol-related diseases cause 5% of the total number of deaths,<sup>55</sup> with more alcohol and substance abuse in sexual minority groups.<sup>51,52,56–58</sup> Four individuals had a diagnosis of alcohol-related diseases before SRS with none after SRS. Further, in the present cohort, two individuals died of the effects of alcohol abuse after SRS. In a previous study on psychiatric morbidity of the present cohort, four diagnoses indicative of alcohol abuse after SRS were found.<sup>46</sup> Alcohol-related diseases are often the consequence of long-lasting alcohol abuse. Therefore, the actual number of individuals in the present cohort with alcohol abuse could be larger.

Four individuals had a diagnosis indicative of chronic lung disease (3.8%). In comparison, 1.3% of individuals older than 35 years in the general Danish population had a diagnosis of severe chronic lung disease.<sup>59</sup> Lung diseases have, to our knowledge, not been investigated previously in individuals with transsexualism, and therefore we lack and call for comparable studies in which to situate our findings.

Somatic morbidity in the present study group could be due to long-term HT and/or, as suggested by numerous previous studies, influenced by poor mental health, low economic status, social exclusion,<sup>60</sup> harassment, negative experiences with school<sup>61</sup> and the employment system,<sup>34,37,62</sup> and discrimination in the health care system.<sup>46,63,64</sup> Thus, previous studies of the present group have found that 50% of the cohort did not complete further education beyond primary and secondary school. Also, at the time of SRS, only 55% were employed<sup>40</sup> and 25% presented with psychiatric morbidity before and after SRS.<sup>46</sup>

For the second study aim (ie, cause of death and its relation to somatic morbidity), the study found that 9.6% of the cohort had died at an average age of 53.5 years, with the main cause of death related to smoking and alcohol abuse. The life expectancy of assigned women and men in Denmark is 81.9 and 78.0 years,

respectively. Previous studies of mortality in transsexual individuals in countries comparable to Denmark<sup>6,10</sup> have found an increased risk of death in transsexual individuals. The present study had a lack of statistical power, and further long-term studies are needed to draw firm conclusions about transsexualism and increased risk of death.

Two individuals in the study group committed suicide 19 and 26 years after SRS, respectively. A Swedish study of SRS individuals (N = 324) found significantly increased mortality from suicide and significantly higher risk for suicide attempts compared with the general Swedish population.<sup>6</sup> A Dutch study (N = 1,109) of SRS and non-SRS individuals found a high incidence of attempted suicide and completed suicide in the study cohort compared with the general Dutch population.<sup>31</sup> An Italian study of 163 SRS MtF individuals found that four had attempted suicide before SRS and one had attempted suicide 12 to 18 months after SRS.<sup>65</sup> A Danish study reported death from suicide in 3 of 29 SRS MtF individuals (follow-up = 6 years).<sup>32</sup> Many explanations can be considered for suicide and attempted suicide. One might be regret for undergoing SRS,<sup>32</sup> but in the present study suicide occurred more than 19 years after SRS and therefore does not seem to be an immediate consequence of SRS. Because reasons for suicide attempts and manifest suicide often are multifactorial and because of the low incidence in the present study, further research is needed to contextualize these results further.

## Limitations

The strength of this study is the unique cohort studied. Thus, on a national basis and over a 30-year period, 98% of all SRS individuals were included. This provides a unique opportunity to assess differences between MtF and FtM individuals on variables for somatic morbidity and mortality. The cohort included only individuals who received permission to undergo SRS during a period with strict criteria for obtaining permission to undergo SRS. Accordingly, the group is highly selected and might not reflect transsexuals per se in Denmark. Although we had a very large cohort for this type of study, some of our statistics had small cell sizes, limited numbers, and thus low statistical power, increasing the chances for type II errors. Because most somatic care in Denmark is provided by general practitioners, an underestimation of the prevalence of somatic morbidity in the study is plausible. Thus, somatic morbidity as presented in this study might be substantially higher.

## CONCLUSION

Using a sample comprised of 98% of all individuals who underwent SRS in Denmark from 1978 through 2010, this study found somatic morbidity in 19.1% of the study group before and 23.2% after SRS. Mortality rates were 9.6%, with an average age at death of 53.5 years. No significant differences in somatic morbidity or mortality were found between MtF and FtM individuals. No firm conclusions can be drawn from the

present study, because the present study design does not allow for determination of causal relations between HT or SRS and somatic morbidity or mortality. One can speculate as to whether the increased risk of psychiatric problems and lifestyle issues in sexual minority groups influenced the risk of mortality and CVD in the present study. The findings underline the importance of supporting individuals with transsexualism to contact and be treated in the public health care system and to pay more attention to lifestyle issues in general.

**Corresponding Author:** Rikke Kildevæld Simonsen, Department of Sexology, University Hospital of Copenhagen, Blegdamsvej 9, Copenhagen 2100, Denmark. Tel: +45-3864-7150; Fax: +45-3864-7164; E-mail: [rikke.kildevaeld@regionh.dk](mailto:rikke.kildevaeld@regionh.dk)

**Conflict of Interest:** The authors report no conflicts of interest.

**Funding:** None.

## STATEMENT OF AUTHORSHIP

### Category 1

#### (a) Conception and Design

Rikke Kildevæld Simonsen

#### (b) Acquisition of Data

Rikke Kildevæld Simonsen

#### (c) Analysis and Interpretation of Data

Rikke Kildevæld Simonsen; Gert Martin Hald

### Category 2

#### (a) Drafting the Article

Rikke Kildevæld Simonsen; Gert Martin Hald; Ellids Kristensen; Annamaria Giraldi

#### (b) Revising It for Intellectual Content

Rikke Kildevæld Simonsen; Gert Martin Hald; Annamaria Giraldi

### Category 3

#### (a) Final Approval of the Completed Article

Rikke Kildevæld Simonsen; Gert Martin Hald; Ellids Kristensen; Annamaria Giraldi

## REFERENCES

- Knudson G, De Cuypere G, Bockting W. Recommendations for revision of the DSM diagnoses of gender identity disorder. *Int J Transgend* 2010; **12**:115-118.
- World Health Organisation. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organisation; 1993.
- World Health Organisation. The ICD-8 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organisation; 1965.
- Ministeriet for Sundhed og Forebyggelse. VEJ nr 10353 af 19/12/2014 Gældende (vejledning om transkønnede). Ministeriet for sundhed og forebyggelse; 2015.
- Sundhedsministeriet (Danish Health Authority). Copenhagen, Denmark: Sundhedsloven [The Danish Health Act]; 2014.
- Dhejne C, Lichtenstein P, Boman M, et al. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011; **6**:e16885.
- Elamin MB, Garcia MZ, Murad MH, et al. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)* 2010; **72**:1.
- Toorians AW, Thomassen MC, Zweegman S, et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. *J Clin Endocrinol Metab* 2003; **88**:5723.
- Laiberte F, Dea K, Duh MS, et al. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2011; **18**:1052.
- Asscherman H, Giltay EJ, Megens JA, et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 2011; **164**:635.
- Turner A, Chen TC, Barber TW, et al. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol (Oxf)* 2004; **61**:560.
- Ruetsche AG, Kneubuehl R, Birkhaeuser MH, et al. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int* 2005; **16**:791.
- Haraldsen IR, Haug E, Falch J, et al. Cross-sex pattern of bone mineral density in early onset gender identity disorder. *Horm Behav* 2007; **52**:334.
- Mueller A, Haeberle L, Zollver H, et al. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med* 2010; **7**:3190.
- Van Caenegem E, Wierckx K, Taes Y, et al. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab* 2012; **97**:2503.
- Merigliola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)* 2015; **83**:597.
- Mueller A, Zollver H, Kronawitter D. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 2011; **119**:95.
- Lapauw B, Taes Y, Simoens S, et al. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone* 2008; **43**:1016.
- De Cuypere G, Elaut E, Heylens G, et al. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *Sexologies* 2006; **15**:126-133.
- Merigliola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)* 2015; **83**:607.
- Gooren LJ, van Trotsenburg MA, Giltay EJ, et al. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *J Sex Med* 2013; **10**:3129.

22. Johansen Taber KA, Morisy LR, Osbahr AJ III, et al. Male breast cancer: risk factors, diagnosis, and management (review). *Oncol Rep* 2010; **24**:1115.
23. Pritchard TJ, Pankowsky DA, Crowe JP, et al. Breast cancer in a male-to-female transsexual. A case report. *JAMA* 1988; **259**:2278.
24. Dimitrakakis C, Bondy C. Androgens and the breast. *Breast Cancer Res* 2009; **11**:212.
25. Somboonporn W, Davis SR. Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev* 2004; **25**:374.
26. Ganly I, Taylor EW. Breast cancer in a trans-sexual man receiving hormone replacement therapy. *Br J Surg* 1995; **82**:341.
27. Gooren LJ, Bowers M, Lips P, et al. Five new cases of breast cancer in transsexual persons. *Andrologia* 2015; **22**:1202-1205.
28. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol* 2013; **169**:471.
29. Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 2008; **159**:197.
30. Gooren LJ, Kreukels B, Lapauw B, et al. (Patho)physiology of cross-sex hormone administration to transsexual people: the potential impact of male-female genetic differences. *Andrologia* 2015; **47**:5.
31. van Kesteren PJ, Asschelman H, Megens JA, et al. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)* 1997; **47**:337.
32. Sorensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand* 1981; **63**:486.
33. De Cuypere G, Janes C, Rubens R. Psychosocial functioning of transsexuals in Belgium. *Acta Psychiatr Scand* 1995; **91**:180.
34. Gomez-Gil E, Trilla A, Salamero M, et al. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav* 2009; **38**:378.
35. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text rev. Arlington, VA: American Psychiatric Association; 2000.
36. Hepp U, Kraemer B, Schnyder U, et al. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res* 2005; **58**:259.
37. Landen M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. *Acta Psychiatr Scand* 1998; **97**:189.
38. Lee JG, Griffin GK, Melvin CL. Tobacco use among sexual minorities in the USA, 1987 to May 2007: a systematic review. *Tob Control* 2009; **18**:275.
39. Shires DA, Jaffee KD. Structural discrimination is associated with smoking status among a national sample of transgender individuals. *Nicotine Tob Res* 2011; **P1**:ntv221. E-pub ahead of print.
40. Simonsen RK, Hald GM, Giraldi A, et al. Sociodemographic study of Danish individuals diagnosed with transsexualism. *Sex Med* 2015; **3**:109-117.
41. Hjerteforeningen. Available at: <http://www.hjerteforeningen.dk/det-goer-vi/hjertetal/hjertetaldk/>. Published 2015. Accessed January 11, 2015.
42. World Health Organization. Promoting mental health. Summary report. Available at: [http://www.who.int/mental\\_health/evidence/en/promoting\\_mhh.pdf](http://www.who.int/mental_health/evidence/en/promoting_mhh.pdf). Published 2004. Accessed January 11, 2015.
43. Rozanski A, Blumenthal JA, Davidson KW, et al. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol* 2005; **45**:637.
44. Albus C, Jordan J, Herrmann-Lingen C. Screening for psychosocial risk factors in patients with coronary heart disease—recommendations for clinical practice. *Eur J Cardiovasc Prev Rehabil* 2004; **11**:75.
45. Morrison C, Woodward M, Leslie W, et al. Effect of socioeconomic group on incidence of, management of, and survival after myocardial infarction and coronary death: analysis of community coronary event register. *BMJ* 1997; **22**:541.
46. Simonsen RK, Giraldi A, Kristensen E, et al. Long-term follow-up of individuals undergoing sex reassignment surgery: psychiatric morbidity and mortality. *Nord J Psychiatry* PMID: 26479779. E-pub ahead of print.
47. European Union Agency for Fundamental Rights. European Union lesbian, gay, bisexual and transgender survey. Vienna, Austria: Publications Office of the European Union; 2013.
48. Sorensen J. Aktiv-passiv Analyse for muskel/skeletsygdomme [Active/passive analysis of muscle and musculoskeletal disease]. Funen, Denmark: Syddansk Universitet; 2005.
49. Taes Y, Lapauw B, Vanbillemont G, et al. Early smoking is associated with peak bone mass and prevalent fractures in young, healthy men. *J Bone Miner Res* 2010; **25**:379.
50. Oyen J, Gram GC, Nygard OK, et al. Smoking and body fat mass in relation to bone mineral density and hip fracture: the Hordaland Health Study. *PLoS One* 2014; **9**:e92882.
51. Santos GM, Rapues J, Wilson EC, et al. Alcohol and substance use among transgender women in San Francisco: prevalence and association with human immunodeficiency virus infection. *Drug Alcohol Rev* 2014; **33**:287.
52. Bloomfield K, Wicki M, Wilsack S, et al. International differences in alcohol use according to sexual orientation. *Subst Abus* 2011; **32**:210.
53. Statens Institut for Folkesundhed. Folkesundhedsrapporten 2007, Kap 6. Copenhagen: Statens Institut for Folkesundhed; 2007.
54. Gooren LJ. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes* 2014; **21**:233.
55. Juel K, Sørensen J, Brønnum-Hansen H. Risikofaktorer og Folkesundhed i Danmark. Copenhagen: Statens Institut for Folkesundhed; 2006.
56. Huebner DM, Thoma BC, Neilands TB. School victimization and substance use among lesbian, gay, bisexual, and transgender adolescents. *Prev Sci* 2015; **16**:734.
57. Drabble L, Trocki KF, Hughes TL, et al. Sexual orientation differences in the relationship between victimization and hazardous drinking among women in the National Alcohol Survey. *Psychol Addict Behav* 2013; **27**:639.

58. Marshal MP, Friedman MS, Stall R, et al. Sexual orientation and adolescent substance use: a meta-analysis and methodological review. *Addiction* 2008; **103**:546.
59. Løkke A, Fabricius P, Vestbo J, et al. Forekomst af kronisk obstruktiv lungesygdom. Copenhagen: Ugeskrift for læger; 2007.
60. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychol Bull* 2003; **129**:674.
61. Terada S, Matsumoto Y, Sato T, et al. School refusal by patients with gender identity disorder. *Gen Hosp Psychiatry* 2012; **34**:299.
62. De Cuypere G, Van HM, Michel A, et al. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry* 2007; **22**:137.
63. Poteat T, German D, Kerrigan D. Managing uncertainty: a grounded theory of stigma in transgender health care encounters. *Soc Sci Med* 2013; **84**:22.
64. Melendez RM, Pinto R. 'It's really a hard life': love, gender and HIV risk among male-to-female transgender persons. *Cult Health Sex* 2007; **9**:233.
65. Imbimbo C, Verze P, Palmieri A, et al. A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. *J Sex Med* 2009; **6**:2736.